REMARKS/ARGUMENTS

Claims 1-36 are pending in the application. Claims 1-30 and 33-36 are canceled without prejudice to subsequent revival. Applicants reserve the right to prosecute these claims in divisional applications. Claims 31 and 32 have been amended. New claims 37-55 have been added. No new matter has been introduced by this amendment. Entry of the amendment and allowance of claims 31, 32 and 37-55 are respectfully requested.

Election/Restriction

New dependent claims 45-49 and 50-54 are drawn to SEQ ID NOS: 2 and 4, respectively. It is respectfully indicated that page 8 was missing from the original restriction requirement mailed on July 16, 2004. Applicants' agent did not address the omission of page 8 in the response to the restriction requirement because it went unintentionally unnoticed. Since the Office Action did not address election of SEQ ID NOS, dependent claims directed to SEQ ID NOS: 2 and 4 are presumed proper.

The Amendment

Claim 31 has been amended to specify that the method is drawn to selecting a molecule which is capable of inhibiting binding of a PI3 kinase protein which binds to a PDGF receptor polypeptide, wherein two analyses are compared to determine the inhibitory effect of the molecule on the binding. Support for this amendment can be found, for example, on page 3, line 17 and 27 and on page 5, lines 20-35. Claim 31 was further amended to specify that the PDGF receptor polypeptide contains at least one phosphorylated tyrosine at position 719 or 708 in its kinase insert (KI) region. Support for this amendment can be found, for example, on page 53, lines 9-26; page 58, lines 20-38; page 59, lines 1-6; page 60, lines 27-38; page 61, lines 1-29; page 62 (see Table 4); and page 63, lines 1-13.

Claim 32 has been amended to correct for proper antecedent basis.

New claim 37 is supported, for example, on page 11, lines 21, 22 and 27; page 5, line 18; and page 10, line 19 of the specification.

New claim 38 is supported, for example, on page 5, lines 20-28.

New claim 39 is supported, for example, on page 44, lines 35-37 and page 45, lines 5-6.

New claim 40 is supported, for example, on page 22, line 17 and throughout the specification.

New claim 41 is supported, for example, on page 5, lines 4-7.

New claim 42 is supported, for example, on page 7, lines 1-9; page 47, lines 1-3; page 58, line 11; and page 1, lines 22-29.

New claim 43 is supported, for example, on page 47, line 8.

New claim 44 is supported, for example, on page 47, lines 11-13.

New claim 45 is supported, for example, on page 19, in Table 2.

New claims 46-49 are supported, for example, on page 15, in Table 1.

New claim 50 is supported, for example, on page 21, in Table 3.

New claims 51-54 are supported, for example, on page 15, in Table 3.

New claim 55 is supported, for example, on page 61, lines 23-24.

Priority

According to the Office Action, the subject matter of claims 31 and 32 has an effective filing date of January 31, 1991 because priority allegedly only reaches back to application number 07/650,794.

However, the application claims priority from application number 07/151,414 which has an effective filing date of February 2, 1988. It is stated for the record, that the Applicants believe that the earlier applications (*i.e.*, application numbers 07/151,414, filed 2.2.88 and 07/309,322, filed 2.10.89) provide support for the instant claim.

Claim Objections

Claims 3, 16, 17 and 28 are objected to because of informalities. These claims have been canceled without prejudice and Applicants reserve the right to correct any informalities during examination of these claims at a later time (*e.g.*, if claims are rejoined or examined on the merits in a divisional application). Hence, the objection is moot.

Rejection Under 35 U.S.C. §112

Claim 31 is rejected under 35 U.S.C. §112, first paragraph, as being allegedly not enabled and described.

The Examiner indicates that the specification is enabling for a method of selecting molecules capable of inhibiting the binding between PI3 kinase and PDGF receptor, however, the specification is allegedly not enabling for a method of selecting molecules capable of inhibiting the binding between all polypeptides and targeted phosphorylated polypeptides. Although this assertion is arguable, Applicants appreciate the Examiner's acknowledgement that the specification is enabling for a method of selecting molecules capable of inhibiting the binding between PI3 kinase and PDGF receptors (at page 4, lines 8-9 of the Office Action). For the sake of prosecution efficiency, the claims have been amended to specify that the method is drawn to selecting a molecule which is capable of inhibiting binding of a "PI3 kinase protein" which binds to a "PDGF receptor polypeptide". Support for this amendment can be found, for example, on page 3, line 17 and 27, on page 5, lines 20-35 and throughout the specification. The claims have further been amended to specify that the PDGF receptor polypeptide contains at least one phosphorylated tyrosine at position 719 or 708 in its kinase insert (KI) region. Support for this amendment can be found, for example, on page 53, lines 9-26; page 58, lines 20-38; page 59, lines 1-6; page 60, lines 27-38; page 61, lines 1-29; page 62 (see Table 4); and page 63, lines 1-13. In light of this amendment, it is believed that the Examiner's concerns are met and the present rejection rendered moot. Thus, Applicants respectfully request that the rejection of claim 31 under 35 U.S.C. §112, first paragraph, for lack of enablement, be withdrawn.

The Examiner further indicates that, with respect to claim 31, the specification is allegedly failing to comply with the written description requirement. As such, the office action asserts that the Applicants have disclosed the claimed method in a more specific manner relating only to PI3 kinase and PDGF receptors. Applicants appreciate the Examiner's indication that the specification is specific to PI3 kinase and PDGF receptors (at page 6, lines 9-10 of the Office Action). Thus, the amended claims meet the written description requirement. As discussed *supra*, the claims have been amended to recite a method which is drawn to selecting a molecule which is capable of inhibiting binding of a "PI3 kinase protein" which binds to a "PDGF receptor

polypeptide." It is believed that the present amendments address the objections of the Examiner. Thus, Applicants respectfully request that the rejection for lack of written description be withdrawn.

The Examiner also indicates that the broad recitation of "analysis and analyses" is not adequately described in the disclosure. Applicants traverse the rejection and submit the specification provides ample support for the term, particularly in the context of the presently pending claims. For example, at page 11, lines 18-29, the specification indicates that the PDGF receptor polypeptide binding may be inhibited by various analogue molecules which can be screened for and purified. On page 46, lines 35-38 and page 47, lines 1-16, the Applicants describe specifically how, for example, transfected cells can be used to evaluate a drug's ability to function as a PDGF agonist or antagonist. Thereby, the cells can be contacted with a test drug and the amount of response can be determined. For example, a PDGF receptor peptide can be added to a solution to see if it can inhibit the binding between the PDGF receptor and PI3 kinase (see page 60, lines 27-30). The inhibition occurs by competition or by interfering with binding on either the receptor or the ligand. Any molecule can be evaluated in this fashion, including peptides, peptide analogous, organic analogue molecules and drugs (see new claim 37). Thus, the Applicants have clearly defined the method and respectfully request that the rejection for lack of written description be withdrawn.

Rejection Under 35 U.S.C. §112

Claim 31 is rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for omitting essential steps such as a correlation step. The Examiner indicates that the Applicants have not indicated what constitutes a positive or negative result of the screening method.

Applicants submit claim 31 has been amended to specify that the analyses are compared to determine the "inhibitory" effect of the molecule on the binding. Assessment of an inhibitory effect is supported throughout the specification. For example, on page 47, lines 11-15 the specification describes that the inhibition of binding will usually occur by competition or by interfering with binding, on either the receptor or the ligand. From the specification it is clear

that an inhibitory effect occurs when the association of the PI3 kinase to the receptor is blocked (*e.g.*, this is explained in detail on page 61, lines 6-29, wherein a series of synthetic peptides were investigated for their ability to block the interaction between the receptor and the PI3 kinase). Thus, Applicants respectfully submit that the claims are clearly defined. Reconsideration and withdrawal of the rejection of claim 31 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection Under 35 U.S.C. §103

Claim 31 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over Kazlauskas *et al.* (*Cell* (1989) 58:1121-1133) in view of Sporn *et al.* (*The Journal of Clinical Investigations* (1986) 78:329-332). The Office Action indicates that Kazlauskas *et al.* teach that autophosphorylation of PDGF receptors results in receptor activation and cellular changes, such as association of cellular polypeptides with the receptor and that the methods used by Kazlauskas *et al.* could be used as a method of screening compounds that inhibit the binding of two polypeptides, which is phosphorylation dependent, with at least one of the polypeptides being autophosphorylated PDGF receptors. The Examiner asserts that the core methods used by Kazlauskas *et al.* such as immunoprecipitation and gel electrophoresis would be sufficient as a screening method although Kazlauskas *et al.* fail to explicitly teach such a use. The Examiner further indicates that Sporn *et al.* teach that PDGF and PDGF receptors are directly implicated in the involvement of several cancers and it would have been obvious for a person of ordinary skill in the art to combine the teachings of Kazlauskas *et al.* and Sporn *et al.* to screen for compounds that inhibit the binding between the two polypeptides with at least one being a PDGF receptor.

To the extent that the rejection applies to the claims as amended the rejection is respectfully traversed.

The Examiner pointed to page 1129, column 2, paragraph 2 of Kazlauskas *et al.* where it is indicated that PDGF stimulation is required for the PDGF receptor to associate with **a number of cell proteins**, including cell proteins of 120, 84, 72 kD and PI3 kinase activity. In fact, Kazlauskas *et al.* further state that **a mutation of Thy-751 to Gly or Phe abolished interaction with the three cell proteins** and PI3 kinase activity. On page 1130, paragraph 1,

Kazlauskas *et al.* state that **autophoshorylation of Tyr-751** provides the signal for a conformational change that allows stable interaction with **a number of cell proteins.** In paragraph 2, it is indicated that polyoma middle T antigen mutants showed that PI kinase association may be necessary to provide a growth stimulus although it may **not** be sufficient. As a matter of fact, there is nothing in Kazlauskas *et al.* that suggests a screening method that is solely based on the interaction of a PDGF receptor polypeptide and PI3 kinase, wherein the PDGF receptor polypeptide contains at least one phosphorylated tyrosine at position 719 or 708 in its kinase insert (KI) region.

In comparison, the Applicants have engaged in extensive research to investigate the interaction of a PDGF receptor polypeptide with a **PI3 kinase**. For example, Applicants have demonstrated that this specific interaction can be blocked with a synthetic PDGF peptide that contains a phosphoryated tyrosine residue at position 719 or 708. In particular, the specification states the following on page 58, lines 30-38 and page 59, lines 1-6:

> "To directly study the interaction between the type B PDGF receptor and PI3 kinase, an in vitro system was established. With this system, it was possible to test the ability of synthetic polypeptides derived from receptor sequences in the kinase insert domain to block interaction of the PI3 kinase with the PDGF receptor. **The interaction could be blocked by a tyrosine-phosphorylated peptide representing a highly conserved region of the kinase insert domain that included tyr (719). However the peptide blocked PI3 kinase binding to the PDGF receptor only when the peptide was phosphorylated on tyrosine.** Scrambled versions of the peptide, even when phosphorylated on tyrosine, had no blocking activity." [Emphasis added.]

The specification states the following on page 61, lines 6-29:

> "To determine the ability of a series of synthetic peptides derived from this sequence to block the interaction between the receptor and the 85 kD/PI3 kinase activity, 3T3 lysates were incubated with the different peptides prior to mixing with immobilized receptor. The results of these experiments are shown in Fig. 4. The first lane of Fig. 4a shows phosphorylated proteins that associated with the wild type receptor in the absence of peptides. The arrow indicates the position of the 85 kD protein that co-purified with the PI3 kinase activity. The other lanes show the proteins that associated with the receptor in the presence of derivatives of the Y719 peptide. See Table 4. **No change in the pattern of receptor-associated protein was seen when the unphosphorylated 719 peptide (Y719) was preincubated with the 3T3 lysate prior to the association with the**

> **receptor. By contrast when a derivative of this peptide that was phosphorylated at position 719 (Y719P) was added to the incubation, it blocked the binding of the 85 kD phosphoprotein (Fig. 4a) and inhibited the association of PI3 kinase activity (Fig. 4b) with the receptor.** A scrambled version of this peptide that contained phosphotyrosine at a position corresponding to 719 but had a rearranged primary sequence failed to block binding of the 85 kD protein and did not prevent the association of PI3 kinase activity with the receptor." [Emphasis added.]

The specification states the following on page 63, lines 5-13:

> "**Surprisingly, a peptide that includes tyrosine at position 719 and phosphotyrosine at position 708 blocked the interaction of PI3 kinase with the receptor (Fig. 4, lane 6).** This finding suggests the possibility that tyrosine 708 is one of the autophosphorylation sites of the receptor that has not yet been mapped. A peptide that included phosphotyrosine at both positions 708 and 719 (Y708P/Y719P) also blocked binding of the 85 kD protein (Fig. 4, lane 8). Short forms of Y708P and Y719P also had blocking activity (Fig. 4 lanes 4 and 9)." [Emphasis added.]

Along the same lines, Sporn *et al.'s* teaching that PDGF ligand is implicated in certain cancers has nothing to do with *an vitro* screening method. It appears that the Office Action is using hindsight in order to combine the teachings of Kazlauskas *et al.* and Sporn *et al.* to allegedly arrive at the instant invention. Notably, neither publication suggests anything that would lead one to think of an *in vitro* screening method that is entirely based on measuring the inhibitory effect that results from blocking the specific interaction of the PDGF receptor with the PI3 kinase, wherein the PDGF receptor polypeptide contains at least one phosphorylated tyrosine at position 719 or 708 in its kinase insert (KI) region. In the absence of the instant invention, there would be truly nothing to suggest such a method. The MPEP 2141 states that the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

The Examiner further rejected claim 31 under 35 U.S.C. §103(a) as being allegedly obvious over Murray *et al.* (U.S. Patent No. 4,766,073) in view of Sporn *et al.* (*The Journal of Clinical Investigations* (1986) 78:329-332).

The Examiner indicates that Murray *et al.* teach a method that utilizes radioactive molecules for detecting binding between PDGF receptors and a test material but does not explicitly teach a screening method. According to the office action, it would be obvious to combine the teachings of Murray *et al.* and Sporn *et al.* because Murray *et al.* provide a method useful for screening compounds that inhibit the binding of PDGF and PDGF receptors, and Sporn *et al.* teach that PDGF is involved in various types of cancers and that antagonists are viable options in fighting disease. The Examiner concludes that the expectation of success would be reasonably assured because molecular biology techniques used by Murray *et al.* are standard techniques with high reproducibility and the method disclosed is conceivably operable in the context of the instant invention.

To the extent that the rejection applies to the claims as amended the rejection is respectfully traversed.

Neither Murray *et al.* nor Sporn *et al.* teach a screening method that utilizes the specific interaction of a PDGF receptor polypeptide and PI3 kinase in order to test for molecules that inhibit the interaction between the PDGF receptor and PI3 kinase, wherein the PDGF receptor polypeptide contains at least one phosphorylated tyrosine at position 719 or 708 in its kinase insert (KI) region. Contrary to the Examiner's suggestion, there is not expectation of success to arrive at the instant invention when combining the two teachings. As indicated in MPEP 2143.03: "All limitation of the claims must be suggested by the combination of references cited as prior art in order to establish *prima facie* obviousness." (*In re Royka and Martin,* 180 U.S.P.Q.580 (CCPA 1974)).

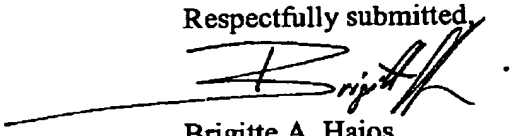
In light of the amendment and arguments presented above, the Applicants respectfully request that the rejection of claim 31 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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